(12) UK Patent Application (19) GB (11) 2 323 594 (13) A

(43) Date of A Publication 30.09.1998

(21) Application No 9706130.3

(22) Date of Filing 25.03.1997

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(51) INT CL^6
C07C 229/30 211/22 215/24 271/22

(52) UK CL (Edition P)
C2C CAA C20Y C200 C236 C286 C30Y C32Y C321 C350 C36Y C360 C361 C366 C368 C43X C45Y C450 C456 C50Y C503 C606 C616 C620 C623 C628 C630 C772 C80Y C802
U1S S1313 S1317 S2411 S2415 S2416

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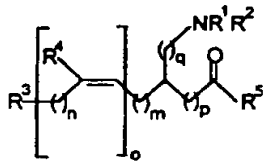
(58) Field of Search
UK CL (Edition O) C2C CLR
INT CL^6 C07C 229/30
ONLINE: CAS-ONLINE, EDOC, JAPIO, WPI

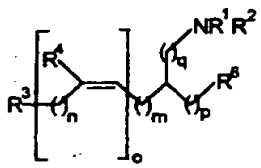
(54) Abstract Title

2-AMINO-ALKANOIC ACID DERIVATIVES, 2-AMINO ALCOHOLS AND DIAMINES

(57) There are disclosed 2-amino-alkanoic and alkenoic acid derivatives, amino alcohols and diamines represented by the general formula (I), (II), (III) respectively and the corresponding products resulting from the hydrogenation of the double bond(s).



(I)



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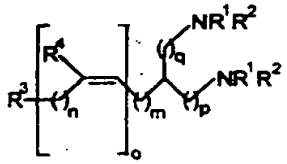

(III)

wherein R^1, R^2 = H, amino protective groups such as benzyl, tert-butoxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl;
wherein R^3 = aromatic, heterocyclic, carbocyclic, linear or branched saturated chain, alkyl carbonyl, alkoxy carbonyl and nitrile;
wherein R^4 = H, alkyl;
wherein R^5 = H, OH, alkyl, alkoxy, NH_2, N-alkyl, or acyl groups;
wherein $m \geq 1$; $n \geq 0$; $o \geq 1$; $p \geq 0$; $q \geq 0$;
their geometrical isomers, their enantiomeric forms, their pharmacologically and immunologically acceptable salts and their uses.

An amino-protected form of methyl 2-amino-eicos-5(z)-enoate was prepared and reduced to the corresponding alcohol and converted to the diamine.

The compounds of formula I, II and III are stated to have pharmacological activity for a wide and diverse range of conditions.

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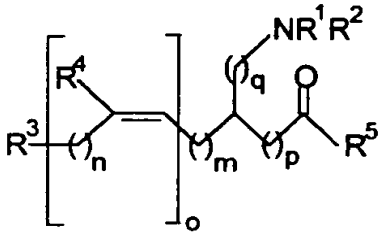
2-AMINO-ALKANOIC ACID DERIVATIVES, 2-AMINO ALCOHOLS AND DIAMINES, THE PROCESSES FOR THEIR PREPARATION AND THEIR USES

The present invention relates to 2-amino-alkanoic and alkenoic acid derivatives represented by the general formula (I) :

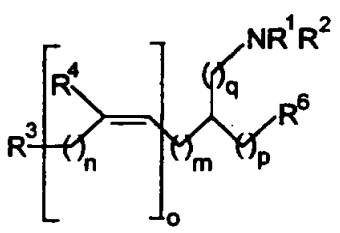


(I)

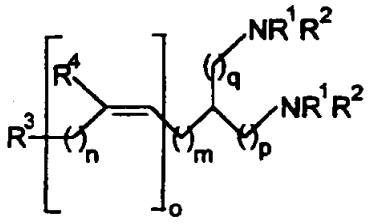
wherein R^1, R^2 = H, amino protective groups such as benzyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl;
wherein R^3 = aromatic, heterocyclic, carbocyclic, linear or branched saturated chain, alkyl carbonyl, alkoxy carbonyl and nitrile;
wherein R^4 = H, alkyl;
wherein R^5 = H, OH, alkyl,alkoxy, NH_2, N-alkyl, or acyl groups;
wherein $m \geq 1$; $n \geq 0$; $o \geq 1$; $p \geq 0$; $q \geq 0$.

The invention extends to the following aspects of compounds of formula (I): (a) their hydrogenated products (resulting from the hydrogenation of the double bonds); (b) their geometrical isomers: (c) their enantiomeric forms; (d) their pharmacologically and immunologically acceptable salts; (e) the processes for their preperation; and (f) the key intermediates for their preparation.

The present invention also relates to 2-amino alcohols and other amino alcohols (and ethers) and 1,2- and 1,3-diamines represented by the general formulae (II) and (III) respectively :



(II)



(III)

wherein R^1, R^2, R^3,R^4, m, n, o, p, q are as defined for formula (I);
wherein R^6 = OH, alkoxy group.

The invention extends to the following aspects of compounds of formulae (II) and (III): (a) their hydrogenated products (resulting from the hydrogenation of the double bonds); (b) their geometrical isomers: (c) their enantiomeric forms; (d) their pharmacologically and immunologically acceptable salts; (e) the processes for their preperation; and (f) the key intermediates for their preparation.

Preferred salts of compounds of formulae (I), (II), (III), are : chloride, acetate, sulfate, tartrate, citrate.

USES

The above compounds exhibit a wide range of biological actions associated with their unique structures and physico-chemical characteristics. Essentially, all resemble natural lipids in being amphipathic, being surfactants, forming monolayers and aggregates.Their biological, chemical and physico-chemical uses are therefore closely linked with these properties. Particularly important is the fact that they are multi-functional possessing a variety of fatty acid (or lipidic or hydrophobic) structures combined with one or more of the common polar groups found in synthetic and natural products and biopolymers (proteins, nucleic acids, sugars and lipids).

A major use therefore is found as agents which have therapeutic properties and immunological properties. Since this is attributable to their structural resemblance to nature's molecules, they should act as inhibitors of membrane processes, particularly all

signalling/signal transduction and ion-channel gating and blocking. Examples may be lipid metabolising enzymes such as phospholipases A_1, A_2, C, D, and the corresponding ether and sphingolipid degrading enzymes, lipases, fatty acid synthetases, lipid methylases and carboxylases, cyclo-oxygenases, lipoxygenases and sterol metabolising enzymes. Conditions associated with the action of these and other enzymes include diabetes, obesity, appetite control, cardiovascular conditions, lipidemias, immuno-disorders, inflammation, analgesia, ageing, diseases associated with abnormal cell growth and differentiation.

Apart from the possibility that they will affect the above biosystems and have therapeutic potential in their own right, some of the amino fatty acids (and analogues and derivatives) can have other uses. The latter are due to their biocompatibility, their adhesion to cell surfaces and membranes and to lipid binding proteins (e.g. albumin). In fact, lipidisation is an established method of increasing bioavailability, delivery and stability of therapeutic substances. Many of the substances depicted are useful in these respects and, additionally, can increase biological lifetimes, cell adhesion and delivery across natural barriers such as skin, gut and blood-brain.

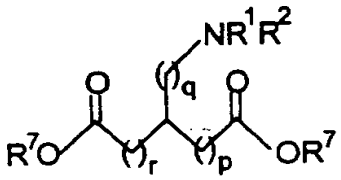
A third possible use involves the properties of aggregation or of mixed aggregation. Many of the above compounds can form liposomes, niosomes or mixed liposomes or mixed niosomes. They can also form the emulsions, lotions, creams, niosomes etc that are useful in the pharmaceutical, immunological and cosmetic industries. Of particular interest is their use in developing novel slow release, microcapsules and other entities.

Their structural resemblance to natural fatty acids (straight chain, branched and unsaturated), lends confidence to their use as pharmaceuticals. In particular, the analogues of the essntial fatty acids (EFAs) may have a range of possible medical use.

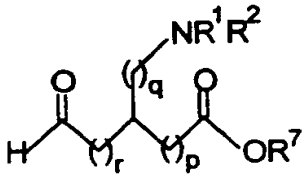
2-Amino alcohols (II) and diamines (III) present antiinflamatory activity in paw edema test, analgesic activity in acetic acid test and cytotoxic activity in MTT test.

SYNTHETIC METHODS

A new method has been developed for the preparation of 2-amino-alkanoic and 2-amino-alkenoic acids. Derivatives (IV) of aspartic and glutamic acid were prepared by the known methods of peptide chemistry (M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, Spinger-Verlag, Berlin, 1984).



(IV)



(V)

Key intermediate derivatives of glutamic and aspartic acid semialdehydes of the general formula (V), wherein R^1, R^2, p, q are as defined for formula (I);

wherein R^7 = alkyl;

wherein $r \geq 1$,

can be prepared by reduction of (IV) with DIBAL (di-isobutyl aluminium hydride), at temperatures lower than -70 ^{0}C in non protic solvents. The double bond nearest to the 2-amino acid moiety of formula (I) is formed by reacting (V) under Wittig conditions. Ylides were generated using K^+ bases, preferable $KN(TMS)_2$, in non-protic solvents.

The saturated compounds were obtained from those with the double bond(s) under standard hydrogenation conditions.

The protective groups R^1, R^2, R^7 of (I) can be removed by the known methods of peptide chemistry (M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, Spinger-Verlag, Berlin, 1984) at the end of the synthesis resulting in salts of 2-amino-alcanoic and 2-amino-alkenoic acids.

N-protected 2-amino-alcanoic and 2-amino alkenoic acids (I) can be converted to amino alcohols (II) and diamines (III) by known procedure [(i) G. Kokotos and C. Noula, *J. Org. Chem.* **1996**, *61*, 6996; (ii) G. Kokotos and V. Constantinou, *J. Chem.*

Res. **1992**, 391(S); (iii) V. Constantinou and G. Kokotos, *Org. Prep. Proc. Int.*, **1994**, *26*, 599].

Examples :

Preparation of Methyl (S)-2-(Di-*tert*-Butoxycarbonyl-amino)-5-oxo-pentanoate. To a stirred solution of dimethyl N,N-Boc_2-*L*-glutamate (10 g, 27 mmol) in dry ether (270 mL) was added dropwise DIBAL (30 mL, 1.0 M in hexane, 30 mmol) at -78°C. The reaction mixture was stirred for 5 min. It was then quenched with H_2O (4 mL) and allowed to warm at rt. The mixture was stirred for 30 min, dried over $MgSO_4$ and filtered through a pad of celite. The solvent was evaporated and the residue was purified by silica gel column chromatography to yield methyl (S)-2-(di-*tert*-butoxycarbonyl-amino)-5-oxo-pentanoate (7.90 g, 85% yield) as an oil : $[\alpha]_D$ -35.3 (c 2.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ : 1.48 (s, 18 H), 2.16 (m, 1 H), 2.52 (m, 2 H), 2.59 (m, 1 H), 3.71 (s, 3 H), 4.87 (dd, J = 9.6, 5.2 Hz, 1 H), 9.76 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ : 22.5 (t), 27.9 (q), 40.5 (t), 52.2 (q), 57.3 (d), 83.4 (s), 152.0 (s), 170.7 (s), 200.9 (d); IR ($CHCl_3$) (cm^{-1}) 3028, 2984, 1789, 1743, 1699, 1370, 1231, 1144, 1121; MS *m/z* (relative intensity) 302 (M - 43) (1), 206 (15), 189 (10), 174 (37), 162 (35), 144 (31), 128 (100), 102 (26), 86 (35). Anal. Calcd. for $C_{16}H_{27}NO_7$: C, 55.64; H, 7.88; N, 4.06. Found: C, 55.45; H, 8.10; N, 4.09.

Preparation of Methyl (2S)-2-*N,N*-Boc_2-eicos-5(Z)-enoate. To a stirred suspension of n-pentadecyl-triphenyl-phosphonium bromide (3.85 g, 7 mmol) in dry toluene (40 mL) at 0 °C was added dropwise KHMDS (12.8 mL, 0.5 M in toluene, 6.4 mmol). The reaction mixture was stirred for 15 min and then cooled to -78°C. After 10 min (S)-2-(di-tert-butoxycarbonyl-amino)-5-oxo-pentanoic acid methyl ester (2 g, 5.8 mmol) dissolved in toluene (5 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The mixture was stirred until TLC showed complete conversion. The reaction was quenched with saturated NH_4Cl (50 mL) solution and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, evaporated and purified by silica gel column chromatography, to yield methyl (S)-2-*N,N*-Boc_2-eicos-5(Z)-enoate (2.7 g, 87% yield)

as an oil: $[\alpha]_D$ -26.2 (c 2.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ : 0.88 (t, J = 6.8 Hz, 3 H), 1.25 (br s, 24 H), 1.49 (s, 18 H), 1.90 (m, 1 H), 2.00 (dd, J = 13.6, 6.8 Hz, 2 H), 2.08 (dd, J = 14, 7.2 Hz, 2 H), 2.15 (m, 1 H), 3.71 (s, 3 H), 4.86 (dd, J = 8.8, 4.8Hz, 1 H), 5.38 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ : 14.1 (q), 22.7 (t), 24.0 (t), 27.3 (t), 27.7 (t), 27.8 (t), 27.9 (t), 28.0 (q), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.6 (t), 29.7 (t), 30.1 (t), 31.9 (t), 52.1 (q), 57.7 (d), 83.0 (s), 128.1 (d), 131.3 (d), 152.1 (s), 171.4 (s); IR ($CHCl_3$) (cm^{-1}) 2928, 2855, 1787, 1787, 1742, 1698, 1458, 1370, 1144; MS *m/z* (relative intensity) 382 $(M - 157)^+$ (4), 366 (9), 339 (30), 280 (83), 156 (10), 143 (25), 133 (100), 106 (24). Anal. Calcd. for $C_{31}H_{57}NO_6$: C, 68.96; H, 10.65; N, 2.60. Found: C, 68.67; H, 10.88; N, 2.65.

Preparation of 2-amino-eicos-5(Z)-en-1-ol. To a stirred solution of 2-(N-*tert*-butoxycarbonylamino)-eicos-5(Z)-enoic acid (0.42 g, 1 mmol) in CH_2Cl_2 (3 mL), kept under a N_2 atmosphere, pyridine (80 μL, 1 mmol) and cyanuric fluoride (180 μL, 2 mmol) were added at -15 °C. The mixture was stirred at -15 °C for 1h and then cold water and CH_2Cl_2 were added. The organic layer was washed with water, dried (Na_2SO_4) and concentrated to a small volume. Sodium borohydride (76 mg, 2 mmol) was added in one portion, followed by dropwise addition of MeOH (2 mL) over a period of 15 min at room temperature. The reaction mixture was neutralized and the organic solvents were removed. EtOAc and water were added, the organic layer was seperated, washed with 1N H_2SO_4 (5 mL) and H_2O (2 x 5 mL) and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography using $CHCl_3$ as eluent.

The *tert*-butoxycarbonyl group was removed by treatment with 4N HCl in tetrahydrofuran (12 mL) for 30 min at room temperature : 0.24g, 71% yield; m.p. 57-58 °C; $[\alpha]_D$ -2.2 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ : 0.85 (t, J = 7 Hz, 3 H), 1.25 (br s, 24 H), 1.65 (m, 2 H), 2.10 (m, 4 H), 3.45 (m, 1 H), 3.75 (m, 1 H), 3.95 (m, 1 H), 5.38 (m, 2 H); FAB MS *m/z* (relative intensity) 312 (M+H) (100), 280 (7). Anal. Calcd. for $C_{20}H_{42}NOCl$: C, 69.03; H, 12.16; N, 4.02. Found : C, 69.04; H, 12.28; N, 4.21.

Preparation of 1,2-eicos-5(Z)-enediamine. To a stirred solution of 2-(N-*tert*-butoxycarbonylamino)-eicos-5(Z)-en-1-ol (0.41 g, 1 mmol) in CH_2Cl_2 (2.5 mL), triethylamine (0.21 mL, 1.5 mmol) and methanesulfonyl chloride (0.12 mL, 1.5 mmol)

were added portionwise. The mixture was stirred at 0 °C for 30 min at room temperature. The organic phase was washed consecutively with brine, 1N H_2SO_4, brine, 5% aq. $NaHCO_3$, brine, dried (Na_2SO_4) and the solvent was removed.

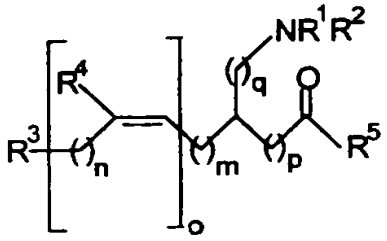
The mesylate was dissolved in DMF (2 mL). Sodium azide (0.20 g, 3 mmol) was added and the mixture heated at 60°C for 6h. The solvent was removed and the residue was taken up in EtOAc (3 x 10 mL). The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel chromatograhy using EtOAc / petroleum ether (1 : 9) as eluent.

To a stirred mixture of the azide and Pd/C (40 mg) in tetrahydrofuran (4 mL), through which N_2 had been passed for 5 min, was added $NaBH_4$ (0.11 g, 3 mmol) and MeOH (8 mL) dropwise. After stirring for 20 min, the catalyst was filtered, the solution was neutralized and the organic solvent was removed. The aqueous phase was extracted with EtOAc (2 x 15 mL) and the organic phase was dried (Na_2SO_4) and evaporated.

The *tert*-butoxycarbonyl group was removed by treatment with 4N HCl in tetrahydrofuran (12 mL) for 30 min at room temperature : 0.18 g, 48% overall yield; m.p. decomp.; $[\alpha]_D$ -12.0 (c 0.5, MeOH); ^{1}H NMR (CD_3OD) δ : 0.85 (t, J = 7 Hz, 3 H), 1.25 (br s, 24 H), 1.65 (m, 2 H), 2.10 (m, 4 H), 3.22 (m, 1 H), 3.51 (m, 1 H), 5.38 (m, 2 H); FAB MS *m/z* (relative intensity) 311 (M+H) (24), 280 (17). Anal. Calcd. for $C_{20}H_{44}N_2Cl_2$: C, 62.64; H, 11.56; N, 7.30. Found : C, 62.61; H, 11.60; N, 7.18.

CLAIMS

1. 2-Amino-alkanoic and alkenoic acid derivatives of general formula (I):



(I)

wherein R^1, R^2 = H, amino protective groups such as benzyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl;

wherein R^3 = aromatic, heterocyclic, carbocyclic, linear or branched saturated chain, alkyl carbonyl, alkoxy carbonyl and nitrile;

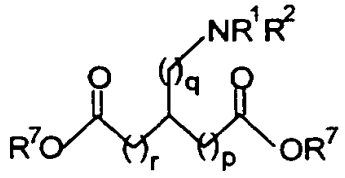
wherein R^4 = H, alkyl;

wherein R^5 = H, OH, alkyl,alkoxy, NH_2, N-alkyl, or acyl groups;

wherein $m \geq 1$; $n \geq 0$; $o \geq 1$; $p \geq 0$; $q \geq 0$;

their salts and processes for their preparation through Wittig type reactions on compounds of general formula (V)

2. Aldehydes of general formula (V) and processes for their preparation through reduction of compound of general formula (IV)



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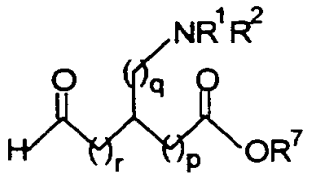


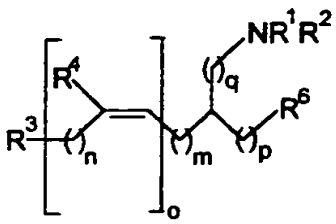
(V)

wherein R^1, R^2, p, q are as defined for formula (I);

wherein R^7 = alkyl;

wherein $r \geq 1$.

3. 2-Amino alcohols of general formula (II) and diamines of general formula (III),



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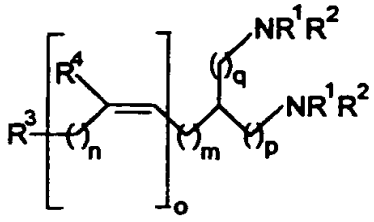

(III)

wherein R^1, R^2, R^3,R^4, m, n, o, p, q are as defined for formula (I);
wherein R^6 = OH, alkoxy group,
and their salts.

4. Compounds according to any of claims 1,2,3 for use in therapy and, in particular, for,:

i) their action on the central and peripheral nervous system, inluding analgesia, anaesthesia, sleep disorders, anxiety, depresion and as anti-convulsants;

ii) the treatment of inflammatory diseases including arthritis and asthma;

iii) the treatment of abnormal cell growth and differentiation, inluding cancer and generative diseases;

iv) diseases of the cardiovascular system;

v) diabetes, obesity, appetite control.

5. Compounds according to any of claims 1,2,3 for use as liposomes, niosomes, microcapsules, lotions, emulsions, creams or other entities used in the pharmaceutical, personal care or cosmetic industries.

The Patent Office

10

Application No:	GB 9706130.3	**Examiner:**	Diane Davies
Claims searched:	1 and 4 & 5 (in part)	**Date of search:**	7 July 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C2C: CLR

Int Cl (Ed.6): C07C 229/30

Other: Online: CAS-ONLINE, EDOC, JAPIO, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	US 4868061 A (Standard Oil Co.) See in particular Example 63.	At least claim 1
X	Chem. Abs. 105: 79318 & Tetrahedron Lett., 27(1), 23-6, (1986) D. Ferroud *et al*, "Synthesis of α-amino acids by catalytic palladium alkylation of Schiffs bases" Discoses a compound of formula I where R^3 is phenyl.	At least claim 1
X	Chem. Abs 122:315057 & J. Org. Chem., 60(7), 2210-15, (1995) M.J. Dunn *et al*, "Synthesis of enantiomerically pure unsaturated α-amino acids using serine derived zinc/copper reagents" Discloses compounds where R^3 is a saturated chain.	At least claim 1
X	Chem. Abs. 110: 8600 & Synthesis, (3), 173-5, (1988) D. Pettig *et al*, "Assymetric syntheis of dimethyl (R)-2-amino-(E)-hept-4-enedioates by the bislatim ether method" Discloses a compound of formula I where R^3 is alkoxycarbonyl.	At least claim 1

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

The Patent Office

11

Application No: GB 9706130.3 **Examiner:** Diane Davies
Claims searched: 1 and 4 & 5 (in part) **Date of search:** 7 July 1997

Category	Identity of document and relevant passage	Relevant to claims
X	Chem. Abs. 109:473862 & Tetrahedron, 43(19), 4297-308, (1987) D.H. Barton *et al*, "Synthesis of novel α-amino acids and derivatives using radical chemistry: syntheisis of amino-adipic and -pimelic acids and appropriate unsaturated derivatives". Discloses various R^3 substitutents.	At least claim 1

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.